Bertaglia, Emanuele; Anselmino, Matteo; Zorzi, Alessandro; Russo, Vincenzo; Toso, Elisabetta; Peruzza, Francesco; Rapacciuolo, Antonio; Migliore, Federico; Gaita, Fiorenzo; Cucchini, Umberto; De Divitiis, Marcello; Iliceto, Sabino; Stabile, Giuseppe

NOACs and atrial fibrillation: Incidence and predictors of left atrial thrombus in the real world

INTERNATIONAL JOURNAL OF CARDIOLOGY, 2017, vol. 249, 179-183

The publisher's version is available at:
10.1016/j.ijcard.2017.07.048

NOACs and Atrial Fibrillation: incidence and predictors of left atrial thrombus in the real world.

Emanuele Bertaglia, Matteo Anselmino^, Alessandro Zorzi, Vincenzo Russo°, Elisabetta Toso^, Francesco Peruzza, Antonio Rapacciuolo**, Federico Migliore, Fiorenzo Gaita^, Umberto Cucchini, Marcello De Divitiis^^, Sabino Iliceto, Giuseppe Stabile*.

Dipartimento di Scienze Cardiache, Toraciche e Vascolari dell'Università di Padova; These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation*Clinica Mediterranea Napoli; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation ^Dipartimento di Scienze Mediche, Città della Salute e della Scienza dell'Università di Torino; These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation °Ospedale Monaldi di Napoli; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation **Università Federico II di Napoli, This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation ^^Ospedale Pellegrini, Napoli - Italy. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Corresponding Author:

Emanuele Bertaglia, MD,

Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Via N. Giustiniani 2,

35121 Padova, Italy

E-mail: bertagliaferro@alice.it

Tel. +39 049 8212332

Fax +39 049 8212509

STRUCTURED ABSTRACT

Aims: despite optimal oral anticoagulation with vitamin K antagonist, left atrial (LA) thrombus could be detected in the left appendage (LAA) in more than 2% of patients with atrial fibrillation (AF) and CHA_2DS_2-VASc score Ó1 but few data are available for patients treated with non-vitamin K antagonist oral anticoagulants (NOACs). We evaluated the occurrence and predictors of LA thrombi by means of transesophageal echocardiography (TOE) in consecutive patients with non-valvular AF who received for at least 3 weeks Apixaban, Dabigatran, or Rivaroxaban.

Methods: this study included 414 consecutive patients (male 252, 60.6%, mean age 67.3 years) referred to our Centers for catheter ablation of AF (n=220, 53.1%) or scheduled electrical cardioversion (n=194, 46.9%). Patients were on Dabigatran (n=160), Rivaroxaban (n=150) or Apixaban (n=104). TOE was performed in all cases within 12 hours prior to ablation or cardioversion.

Results: preprocedural TOE revealed LA thrombus in 15/414 patients (3.6%), all located in the LAA (Apixaban 3/104 2.9%, Dabigatran 5/160 3.1%, and Rivaroxaban 7/150 4.7%, p=0.69). Of these, 14 patients had persistent AF. Patients with LAA thrombus had a mean CHA_2DS_2-VASc score of 3 (3-4). Higher CHA_2DS_2-VASc score (p=0.02), but not the type of NOAC, significantly predicted the presence of LA thrombus.

Conclusion: the incidence of LAA thrombus in a cohort of patients anticoagulated with NOACs is low but not negligible, in any case similar among the 3 drugs. Preprocedural TOE should be considered in patients with a CHA2DS2-VASc score > 3.

KEY-WORDS: atrial fibrillation; non-vitamin K antagonist oral anticoagulants; left atrial thrombus; transesophageal echocardiography.

1. *INTRODUCTION*

Atrial fibrillation (AF) is the most frequently sustained cardiac arrhythmia, with a prevalence of about 2-3% in the general population.(1) Cardioversion (both electric and pharmacological) in patients with AF is associated with a risk of systemic embolism ranging from 5% to 7% without adequate anticoagulation.(2) Vitamin K antagonist therapy significantly reduced the risk of thromboembolic events (0.7% to 0.8%).(3) For patients with AF of $\geq$ 48 hours duration, current Guidelines recommend adequate anticoagulation for at least 3 weeks before and 4 weeks after cardioversion(1). However, previous studies suggest that the incidence of left atrial (LA)/LA appendage (LAA) thrombus under treatment with vitamin K antagonist (VKAs) ranges between 0.6 and 7%.(4-6)

Novel oral anticoagulants (NOACs) are alternatives to vitamin K antagonist therapy for long-term stroke prevention in patients with non-valvular AF.(7-10) However, there are still underexplored aspects related to the management of patients on NOACs. Specifically, estimates of the prevalence of LA/LAA thrombus after adequate anticoagulation with NOAC are mainly based on randomized trials whereas ñreal lifeò data are lacking.(11-14) Transesophageal echocardiogram (TOE) is a moderately invasive method that allows a detailed evaluation of the structure and function of the LAA. It is accurate and the gold standard for identifying or excluding LA/LAA thrombus.(15) Therefore, we designed this study to assess prevalence and predictors of LAA thrombus at TOE performed before elective electrical cardioversion or catheter ablation for AF in patients treated with different NOACs.

2. *METHODS*

2.1 Setting. This multicenter study enrolled consecutive patients (18 years or older) with a CHA_2DS_2-VASc score $\geq$ 1, who underwent TOE before scheduled electrical cardioversion or ablation for AF at 6 Italian Centers (University Hospital, Padova; Clinica Mediterranea, Napoli; University Hospital, Torino; Ospedale Monaldi, Napoli; Federico II University Hospital, Napoli;

Pellegrini Hospital, Napoli) from January 2015 to May 2016 on NOAC therapy with Apixaban, Dabigatran, or Rivaroxaban (Edoxaban was not commercially available in Italy at the time of the study).

Exclusion criteria were AF due to a reversible cause (e.g., hyperthyroidism, infection, transient perioperative AF), moderate or severe mitral valve stenosis, mechanical heart valve, heart transplant, need for aspirin at a dose of >100 mg/day or dual antiplatelet therapy, active liver disease, calculated creatinine clearance of <30 ml per minute, pregnancy, stroke within 14 days, LA thrombus documentation within 3 months, off-label drug dosages and non-compliance with drug therapy.

This retrospective observational study was approved by our institutional review committees, and all subjects gave written informed consent.

2.2 Clinical evaluation. Type of AF (paroxysmal or persistent, according to definition of 2016 ESC Guidelines),(1) medical background of patient (in particular the presence of structurally heart disease or coronary artery disease), and CHA_2DS_2-VASc score of all subjects were evaluated.

2.3 Management of anticoagulation therapy. All study patients were anticoagulated with Apixaban, Dabigatran, or Rivaroxaban for at least 3 weeks and performed TOE within 12 hours from the last intake of the drug. Patients scheduled for catheter ablation withdrawn Apixaban and Dabigatran 12 hours, and Rivaroxaban 24 hours before ablation.

2.4 Echocardiographic evaluation. All included patients were studied by transthoracic and transoesophageal (TOE) echocardiogram (Vivid E9, GE HVingmed, Horten, NO; iE33 xMATRIX, Philips, Andover, MA, USA)). Echocardiographic measurements were performed according to the current recommendations.(16) Transthoracic echocardiogram was performed on the day before or on the same day of the procedure using a 1.5ï 4.6 MHz (M5S-D and M5Sc-D, GE Vingmed) or a 1.0-5.0 MHz (S5-1, Philips) imaging transducer.

TOE was performed within 12 hours prior to catheter ablation or just before electrical cardioversion. Blood pressure, heart rate, and oxygen saturation were continuously monitored. A 3.0ï 8.0 MHz multiplane phased array transducer (6VT-D, GE Vingmed; or X7-2T, Philips) was used. In particular, cine loops of the LA appendage were obtained during stepwise rotation of the imaging sector in 5-10 degree increments from 0 to 180 degrees during continuous visualization of the LA appendage. LA thrombus was defined as an echodense intracavitary mass distinct from the underlying endocardium and not caused by pectinate muscles.(17)

2.5 Statistical analysis. Data are expressed as mean±SD or median with 25 to 75 percentiles for normally distributed and skewed variables, respectively. Normality was assessed with the Shapiro-Wilk test. To assess differences among the 3 groups, categorical variables were compared with the ^{2} test while continuous variables were compared with the Kruskall-Wallis Test. Post-hoc comparisons between 2 groups were performed using the Bonferroni correction. A value of $P < 0..05$ was considered significant. Because of the small number of events multivariate analysis was not performed. Statistics were analyzed with SPSS version 19 (SPSS, Inc, Chicago, IL).

3. RESULTS

3.1 Clinical data. Data from 414 consecutive patients on NOAC referred for AF catheter ablation (n=220 53,1%) or scheduled electrical cardioversion (n=194, 46.9%) were collected. All patients were anticoagulated with NOAC: Apixaban (n=104, 25.1%), Dabigatran (n=160, 38.7%), and Rivaroxaban (n=150, 36.2%). A low NOAC dose of was taken by 18 (4.3%) patients. Clinical data are shown in Table 1.

3.2 Echocardiographic data. Echocardiographic data are shown in Table 1. The mean LA volume resulted of 80.9 ml. At TOE, a thrombus was present in 15 patients (3.6%), always located in the LAA.

3.3 Characteristics of patients with thrombus at TOE. Patients with LAA thrombus had a mean CHA_2DS_2-VASc score of 3 (3-4), a mean LA volume of 78 ml (39-148 ml), and 14/15 patients had persistent AF. Only 1 patient took a low NOAC dose (Dabigatran 220 mg daily).

Patients with LAA thrombus showed a significantly higher CHA_2DS_2-VASc score than patients without (p=0.02) (Table 2). In particular, a CHA_2DS_2-VASc score > 3 was present in 6 patients.

Among variables of CHA_2DS_2-VASc score, only history of heart failure, diabetes, and previous stroke/TIA predicted the presence of LAA thrombus.

3.4 Comparison among NOACs. Clinical and echocardiographic characteristics of patients on Apixaban, Dabigatran, and Rivaroxaban were similar (Table 3). A LAA thrombus was found in 3/104 (2.9%) patients on Apixaban, 5/160 (3.1%) patients on Dabigatran, and 7/150 (4.7%) patients on Rivaroxaban (p=0.69).

3.5 Thromboembolic complications and management of patients with LAA thrombus. Among the 399 patients without LAA thrombus at TOE we did not observe any embolic complication during or after electrical cardioversion or catheter ablation. In the 15 patients with LAA thrombus the scheduled procedure was not performed, NOAC was substituted with full dose enoxaparin (100 UI per kg bid) imbricated with warfarin, with the aim to maintain an INR between 2.5 and 3.5. After 4 to 8 weeks of anticoagulation with warfarin the thrombus disappeared and the scheduled procedure was performed in all but one patients. We did not observe embolic complications in any of these 15 patients.

4. DISCUSSION

4.1 Main findings. 1) In a cohort of patients anticoagulated with NOACs the incidence of LAA thrombus was low but not negligible. 2) The incidence of LAA thrombus appeared similar among patients treated with Apixaban, Dabigatran, and Rivaroxaban. 3) Preprocedural TOE should be considered in patients with a CHA_2DS_2-VASc score > 3.

4.2 Incidence of LA thrombus on anticoagulation therapy. Systemic and cerebral thromboembolism is one of the most feared complications of AF. In patients scheduled for elective cardioversion for AF >48 hours of duration current Guidelines recommend a sufficient therapeutic anticoagulation least 3 weeks before the procedure.(1)

Previous studies in patients treated with VKAs reported an incidence of systemic embolism in anticoagulated patients undergoing elective cardioversion of about 1%. In the RE-LY trial (Dabigatran vs. VKAs), a cardioversion was performed in 1270 patients. Stroke or systemic embolism at 30 days after cardioversion occurred in 0.8%, 0.3%, and 0.6% of patients receiving Dabigatran 220mg daily, Dabigatran 300mg daily, and VKAs, respectively.(7) In the ROCKET-AF trial (Rivaroxaban vs. VKAs), cardioversion or catheter ablation was carried out only in 364 patients. The occurrence of stroke or systemic embolism was reported only at the end of the follow-up, and resulted respectively of 1.88 % and 1.86% in patients receiving Rivaroxaban and VKAs.(8) Two recent studies specifically address NOAC for cardioversion. In the X-VeRT trial 1504 patients receiving cardioversion were randomized to VKAs or Rivaroxaban. Stroke or systemic embolism at 30 days after cardioversion occurred in 1.02% of patients on VKAs and in 0.51% of patients on Rivaroxaban.(14) More recently, ENSURE-AF trial randomized 2199 patients waiting for cardioversion to VKAs or Edoxaban. The primary efficacy composite endpoint of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality occurred in 1.0% of patients of both arms.(18)

The results of the above-mentioned studies suggest that the risk of systemic embolism in elective cardioversion is not negligible and this may be the result of persistent LA/LAA thrombus despite adequate anticoagulation. TOE is a moderately invasive method that allows a detailed evaluation of the structure and function of the LAA. It is accurate and the gold standard for identifying or excluding LA/LAA thrombus.) The incidence of LAA thrombus under treatment with VKAs depends on the patient population studied and on the time on therapeutic range: however, in most studies on patients treated with VKA the incidence of LAA thrombus was between 0.6 and

7 %.(4-7,9,14,19) In the present study of real world, we observed a 3,6% incidence of LAA thrombus among 414 patients treated with NOAC, a figure which is similar to previous studies in patients with VKAs.

4.3 Comparison among NOACs. According to our study, LAA thrombus occurred in 2.9% of patients on Apixaban, in 3.1% of patients on Dabigatran, and in 4.7% of patients on Rivaroxaban. In the Literature, most of the data about the rate of LAA thrombus in patients on NOACs comes from Dabigatran and Rivaroxaban. Including our data (Figure 1), 751 patients on Dabigatran 220 mg or 300 mg daily,(11, 20-22) 608 patients on Rivaroxaban 15 or 20 mg daily,(14, 20-22) and 280 patients on Apixaban 5 or 10 mg daily (13, 22) were evaluated with TOE after at least 3 weeks of anticoagulation. The incidence of LAA thrombus was similar between Apixaban (3/280, 1.1%) and Dabigatran (11/751, 1.4%), while slightly higher for Rivaroxaban (19/608, 3.1%). This result was mainly due to the very high occurrence of LAA thrombi (18.2%) in the 33 patients enrolled in the X-VeRT trial who underwent TOE before elective cardioversion.(14) Of note, only å10% of patients scheduled for elective cardioversion in the X-vert trial underwent TOE but the reasons for the choice were not provided: lack of adherence in taking Rivaroxaban might be one, and this could have reduced the anticoagulant effect of Rivaroxaban.

4.4 Predictors of LAA thrombus. Our results support previous work showing that the $CHADS_2$ and CHA_2DS_2-VASc scores predict the presence of LAA thrombus in patients before AF ablation. (4,5,21-22) In particular, history of heart failure, diabetes, and previous stroke/TIA identified patients with LAA thrombus. $CHADS_2$ and CHA_2DS_2-VASc score demonstrated to be useful for predicting thromboembolic events and mortality after catheter ablation for AF.(6,23) So, it is not surprising that patients with a very high risk score for thromboembolism could be refractory to standard anticoagulation.

On the contrary, we did not confirm the role of LA dimension as predictor of LAA thrombus (4,5,21). This discrepancy could be explained by the different method of measuring LA size: LA diameter in previous studies, LA volume in our study.

5. *STUDY LIMITATIONS*.

The study had a retrospective, non randomized design. The relatively small number of patients investigated in this study impeded to perform a comparison among NOACs with a statistically significant power. Logistic regression was not calculated for individual comparisons owing to the low event rate. We enrolled a selected cohort of AF patients, that undergo rhythm control strategy. Therefore, our results cannot be extrapolated to all AF patients. Further studies should address the present issues in a larger patient cohort including Edoxaban patients.

We have not clear explanations of the effect of warfarin on LAA thrombi. The simplest interpretations of this phenomenon are: 1) warfarin has a stronger anticoagulant power than NOACs when a high INR level is maintained; 2) thrombi, we do not know if they were already present when NOAC started, sometime need more time to dissolve.

6. ***CONCLUSIONS.***

The incidence of LAA thrombus in a cohort of patients anticoagulated with NOACs is low but not negligible, in any case similar among Apixaban, Dabigatran, and Rivaroxaban. Patients with a CHA_2DS_2-VASc score > 3 showed a higher chance of LAA thrombus suggesting that preprocedural TOE should be considered in these individuals.

REFERENCES

1. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. *Europace* 2016;18:1609-1678
2. Arnold AZ, Mick MJ, Mazurek RP, Loop FD, Trohman RG. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. *J Am Coll Cardiol*. 1992;19:851-855.
3. Steering and Publications committees of the ACUTE Study. Design of a clinical trial for the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE multicenter study). *Am J Cardiol*. 1998;81:877ï 883.
4. Scherr D, Dalal D, Chilukuri K, Dong J, Spragg D, Henrikson CA, et al. Incidence and predictors of left atrial thrombus prior to catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2009;20:379ï 384.
5. Wallace TW, Atwater BD, Daubert JP, Voora D, Crowley AL, Bahnson TD, et al. Prevalence and clinical characteristics associated with left atrial appendage thrombus in fully anticoagulated patients undergoing catheter-directed ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2010;21:849-852.
6. Anselmino M, Garberoglio L, Gili S, Bertaglia E, Stabile G, Marazzi R, et al. Left atrial appendage thrombi relate to easily accessible clinical parameters in patients undergoing atrial fibrillation transcatheter ablation: A multicentre study. Int J Cardiol 2017; doi: 10.1016/j.ijcard.2017.04.014.
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139ï 1151.

8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883ï 891.
9. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al, ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981ï 992.
10. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL,et al, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093ï 2104.
11. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation 2011;123:131ï 136.
12. Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, et al. Outcomes following cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. J Am Coll Cardiol 2013;61:1998ï 2006.
13. Flaker G, Lopes RD, Al Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). J Am Coll Cardiol 2014;63:1082ï 1087.
14. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma C-S, Le Heuzey J-Y, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J 2014;35:3346-3355.
15. Beigel R, Wunderlich NC, Ho SY, Arsanjani R, Siegel RJ. The left atrial appendage: anatomy, function, and noninvasive evaluation. JACC Cardiovasc Imaging. 2014;7:1251ï 1265.

16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiographyôs Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiographyôs Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-1463.
17. Shanewise JS, Cheung AT, Aronson S, Stewart WJ, Weiss RL, Mark JB, Savage RM, Sears-Rogan P, Mathew JP, Quinones MA, Cahalan MK, Savino JS. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anestesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. J Am Soc Echocardiogr 1999;12:884-900.
18. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, et al; ENSURE-AF investigators. Edoxaban versus enoxaparinï warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. Lancet. 2016 Oct 22;388 .
19. Dorenkamp M, Sohns C, Vollmann D, Lüthje L, Seegers J, Wachter R, et al. Detection of left atrial thrombus during routine diagnostic work-up prior to pulmonary vein isolation for atrial fibrillation: role of transesophageal echocardiography and multidetector computed tomography. Int J Cardiol. 2013;163:26ï 33.

20. Reers S, Agdirlioglu T, Kellner M, Borowski M, Thiele H, Waltenberger J, et al. Incidence of left atrial abnormalities under treatment with dabigatran, rivaroxaban, and vitamin K antagonists. Eur J Med Res 2016; 21:41-50.
21. Zylla M, Pohlmeier M, Hess A, Mereles D, Kieser, M, Bruckner B, et al. Prevalence of Intracardiac Thrombi Under Phenprocoumon, Direct Oral Anticoagulants (Dabigatran and Rivaroxaban), and Bridging Therapy in Patients With Atrial Fibrillation and Flutter. Am J Cardiol 2015;115:635-640.
22. Wyrembak J, Campbell KB, Steinberg BA, Bahnson TD, Daubert JP, Velazquez EJ, et al. Incidence and Predictors of Left Atrial Appendage Thrombus in Patients Treated With Non vitamin K Oral Anticoagulants Versus Warfarin Before Catheter Ablation for Atrial Fibrillation. Am J Cardiol 2017;119:1017-1022.
23. Chao TF, Lin JY, Tsao H-M, Tsai C-F, Lin W-S, Chang S-L, et al. CHADS2 and CHA2DS2-VASc Scores in the Prediction of Clinical Outcomes in Patients With Atrial Fibrillation After Catheter Ablation. J Am Coll Cardiol 2011;58:2380ï 2385.

TABLES

Table 1: Clinical and echocardiographic characteristics of the 414 study patients.

Male gender (%)	252 (61%)
Age (years)	67±1.2
Arterial hypertension (%)	218 (53%)
Coronary artery disease	73 (18%)
Left atrial volume (ml)	80,9
Congestive heart failure (%)	11 (2,6%)
Vascular disease (%)	81 (19,6%)
Paroxysmal AF (%)	53 (13%)
Diabetes (%)	69 (16,7%)
Previous stroke/TIA (%)	30 (7,2%)
CHA_2DS_2-VASc score	2.6±1.2
AF at TOE (%)	239 (57,7%)
Thrombus at TOE (%)	15 (3,6%)

Data are presented as mean (SD), unless otherwise indicated. AF=atrial fibrillation;

TOE=transesophageal echocardiogram.

Table 2: Univariate analysis for comparisons between patients with and without LAA thrombus at TOE.

	No Thrombus N=399	**Thrombus N=15**	**p**
Mean age	68 (60-74)	73 (62-73)	0.72
Males	239 (60%)	12 (80%)	0.18
CHA_2DS_2VASc	2 (2-3)	3 (3-4)	0.013
$CHA_2DS_2VASc>3$	88 (22%)	7 (47%)	0.026
Arterial Hypertension (%)	261 (66%)	6 (40%)	0.07
Coronary artery disease	73 (18%)	4 (27%)	0.50
LA volume (ml)	75 (57-103)	78 (39-148)	0.72
Congestive heart failure (%)	7 (1,7%)	4 (26,6%)	0,001
Vascular disease (%)	77 (19,4%)	4 (26,7%)	0,50
Diabetes (%)	63 (15,9%)	6 (40%)	0,014
Previous stroke/TIA (%)	26 (6,6%)	4 (26,7%)	0,03
Paroxysmal AF	52 (13%)	1 (6.7%)	0.70
Type of NOAC Dabigatran Rivaroxaban Apixban	 154 (39%) 143 (36%) 101 (25%)	 5 (3.1%) 7 (4.7%) 3 (2.9%)	 0.69
Low NOAC dose	17 (4%)	1 (7%)	0.49

Data are presented as mean (SD), unless otherwise indicated.

AF=atrial fibrillation; TOE=transoesophageal echocardiogram

Table 3: Clinical and echocardiographic characteristics of patients on Apixaban, Dabigatran, and Rivaroxaban.

					Among groups	***Post-Hoc (Bonferroni)***		
	Overall N=414	**Dabigatran N=160**	**Rivaroxaban N=150**	**Apixaban N=104**	**p**	***p (D vs R)***	***p (D vs A)***	***p (R vs A)***
Mean age (years)	67±1.2	66.7±9.8	67.2±10.6	68.3±9.5	0.49			
Males	252 (61%)	97 (61%)	86 (57%)	69 (66%)	0.34			
CHA_2DS_2VASc	2.6±1.2	2.4±1.2	2.7±1.3	2.8±1.2	**0.04**	*0.30*	***0.04***	*0.34*
$CHA_2DS_2VASc>3$	95 (23%)	30 (19%)	42 (28%)	23 (22%)	0.15			
Arterial Hypertension (%)	218 (53%)	54 (34%)	95 (63%)	69 (66%)	0.90			
Coronary artery disease (%)	77 (19%)	25 (16%)	27 (18%)	25 (24%)	0.24			
Left atrial volume (ml)	80,9	85±39	80±32	76±30	0.16			
Congestive heart failure (%)	11 (2,6%)	5 (3,1%)	2 (1,3%)	4 (3,8%)	0,23			
Vascular disease (%)	81 (19,6%)	26 (16,5%)	29 (19,5%)	26 (25%)	0,23			
Diabetes (%)	69 (16,7%)	27 (17,1%)	25 (16,8%)	17 (16,3%)	0,9			
Previous stroke/TIA (%)	30 (7,2%)	9 (5,7%)	9 (6,0%)	12 (11,5%)	0,16			
Paroxysmal AF (%)	53 (13%)	30 (19%)	12 (8%)	11 (7%)	**0.01**	***0.015***	*0.21*	*1.0*
Low NOAC dose	18 (4.3%)	14 (9%)	4 (3%)	0	**<0.001**	*0.06*	***0.002***	*0.30*
LAA Thrombus	15 (3.6%)	5 (3.1%)	7 (4.7%)	3 (2.9%)	0.69			

Data are presented as mean (SD), unless otherwise indicated. AF=atrial fibrillation; TOE=transesophageal echocardiogram.

FIGURE LEGEND

Figure 1: LAA thrombus in patients on Dabigatran, Rivaroxaban, and Apixaban in the Literature.